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Review

Does the oxysterol 27-hydroxycholesterol underlie Alzheimer's disease–Parkinson's disease overlap?

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ABSTRACT

Alzheimer's disease (AD), the most common form of dementia, is characterized histopathologically by the deposition of β-amyloid (Aβ) plaques and neurofibrillary tangles-containing hyperphosphorylated tau protein in the brain. Parkinson's disease (PD), the most common movement disorder, is characterized by the aggregation of α-synuclein protein in Lewy body inclusions and the death of dopaminergic neurons in the *substantia nigra*. Based on their pathological signatures, AD and PD can be considered as two different disease entities. However, a subpopulation of PD patients also exhibit Aβ plaques, and AD patients exhibit α-synuclein aggregates. This overlap between PD and AD suggests that common pathological pathways exist for the two diseases. Identification of factors and cellular mechanisms by which these factors can trigger pathological hallmarks for AD/PD overlap may help in designing disease-modifying therapies that can reverse or stop the progression of AD and PD.
For the last decade, work in our laboratory has shown that fluctuations in the levels of cholesterol oxidation products (oxysterols) may correlate with the onset of AD and PD. In this review, we will provide results from our laboratory and data from literature that converge to strongly suggest the involvement of cholesterol and cholesterol oxidation products in the pathogenesis of AD and PD. We will specifically delineate the role of and the underlying mechanisms by which increased levels of the oxysterol 27-hydroxycholesterol contribute to the pathogenesis of AD, PD, and AD/PD overlap.

1. Introduction

Alzheimer's disease (AD) is a complex and heterogeneous disorder that presently affects more than 4 million citizens in the U.S., and is projected to affect more than 14 million people within the next 50 years if no cure is found. Present "treatment approaches" are, at best, modestly helpful in stabilizing clinical symptoms for a limited duration. Because of the devastating nature, the increasing prevalence and the subsequent social and economic burden of AD, research into the pathogenesis of this disorder is a major health priority. The research effort deployed for the last decades has led to the identification of genetic defects related to the familial forms of AD. Subsequently to the identification of these genes, various cellular and animal models were designed. These models have helped in understanding aspects of the pathophysiology of the early-onset familial forms of AD. However, the causes of the sporadic late-onset forms of AD (LOAD), which represent the vast majority of AD cases, remain to be identified.

Parkinson's disease (PD) is the most common movement disorder and the second common progressive neurological disorder after AD. PD affects people over the age of 50 and, in most cases, PD patients become severely disabled. It is estimated that about 1 million people in the United States have PD. In addition to the disabling effects and the emotional toll related to PD, management of this disease is costly to society. The total cost is estimated to exceed $6 billion annually and this cost is anticipated to increase as the population gets older. Currently, there is no cure for PD, and most of the available drugs can at best manage the symptoms associated with the disease. Unfortunately, the long-term use of these symptomatic treatments is associated with adverse effects including motor fluctuations and cognitive symptoms. The search for efficacious therapies that can prevent, reverse or stop the progression of PD would benefit from a better understanding of the pathogenesis of this disease.

Accumulation of β-amyloid (Aβ) peptide and hyper-phosphorylation of tau protein are the two major pathological hallmarks of AD. Cellular pathways that control Aβ and phosphorylated tau levels are of particular interest for the search of agents that reduce Aβ and phosphorylated tau accumulation and ultimately reduce the progression of AD. On the other hand, PD is characterized by the death of dopaminergic neurons in the *substantia nigra* and the aggregation of α-synuclein protein in Lewy body inclusions in the brain. As such, AD and PD can be seen as two distinct pathologies. However, a large number of AD patients also have α-synuclein deposition and a subset of PD population accumulates Aβ in the brain. The distribution of Lewy bodies in AD occurs mostly in the

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amygdala, where Lewy bodies are observed in approximately 60% of both sporadic and familial AD (Choi et al., 2012; Kotzbauer et al., 2001). This overlap strongly suggests that specific pathological pathways converge to trigger common hallmarks of both AD and PD in same brain. In addition to the histopathological post mortem overlap between AD and PD, both AD patients and PD patients develop similar disorders including severe depression, hallucination, and psychosis at the advanced stages of the disease. Thus, it may be possible that specific triggers act on cellular pathways that converge to induce abnormalities that are common to AD and PD. In this review, we will attempt to demonstrate that cholesterol metabolism dyshomeostasis may be a common pathological event that leads to both AD and PD progression as well as potential AD and PD overlap. Work by others and from our laboratory for the last ten years points to the cholesterol oxidation product (oxysterol) 27-hydroxycholesterol (27-OHC) as a potential functional link between dysregulation in cholesterol metabolism and AD/PD pathology.

2. Oxysterol homeostasis in the brain

Cholesterol is an essential molecule in that it regulates a wide variety of functions including a role in the plasma membrane architecture. The brain makes the cholesterol it needs independent of the peripheral cholesterol pool. In the brain, cholesterol is removed by conversion to the oxysterol 24-hydroxycholesterol (24-OHC) via the cytochrome P450 CYP enzyme (CYP46A1) that is expressed exclusively in the brain, primarily in neurons and some astrocytes. On the other hand, the oxysterol 27-hydroxycholesterol (27-OHC) is the major cholesterol metabolite in the circulation and is synthesized by almost all cells from cholesterol by the CYP27A1 enzyme. Circulating 27-OHC levels are 0.15–0.73 μM, and these concentrations can be in the millimolar range in some pathological situations such as atherosclerosis (Brown and Jessup, 1999). 27-OHC is also made in the brain as the CYP27A1 gene is expressed in the brain in neurons, astrocytes and oligodendrocytes, but at very low concentrations (Brown et al., 2004). Conversely to cholesterol that does not cross the blood brain barrier (BBB), both 27-OHC and 24-OHC have the ability to cross into and out of the brain (Lutjohann et al., 1996). Currently, the role of oxysterols and the extent to which these cholesterol oxidation products are important to the pathogenesis of AD/PD are not defined. Oxysterol homeostasis in the brain is tightly regulated with specific levels maintained in various brain regions. For example, the 27-OHC: 24-OHC ratio is of ~1:8 in the frontal cortex, 1:5 in the occipital cortex, and 1:10 in the basal ganglia (Heverin et al., 2004). While there exists a normal physiological need for conversion of cholesterol to 27-OHC and 24-OHC as a route of elimination of cholesterol, increased levels of 27-OHC in the brain may have widespread pathological ramifications. Indeed, excessive formation of 27-OHC occurs following hypercholesterolemia and also oxidative stress, a condition found to accelerate conversion of even normal basal levels of cholesterol to oxysterols (Infante et al., 2010; Vaya et al., 2007). Thus, under oxidative stress conditions, normal levels of cholesterol, either in the peripheral system or in the brain, can be converted to 27-OHC, that when accumulated in the brain alters the 27-OHC: 24-OHC ratio. Alterations in this ratio may have deleterious consequences that increase the risk for AD/PD.

3. AD and cholesterol metabolism

The finding by Corder et al., 1993 that the ε4 allele of the apolipoprotein E (ApoE) gene is associated with a high incidence of late-onset AD suggests that disturbances in cholesterol homeostasis are a potential risk for AD. Indeed, ApoE is a major transporter of both peripheral and brain cholesterol, and carrying of ApoE ε4 in humans is associated with high plasma cholesterol incidence (Eto et al., 1988). The discovery by Sparks and colleagues (1994) that rabbits fed with high cholesterol diets exhibit cerebral β-amyloid (Aβ) plaques reinforced the cholesterol-AD link hypothesis (Sparks et al., 1994). Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model (Refolo et al., 2000). Additionally, processing of the amyloid-β precursor protein (AβPP) by BACE1 yielding Aβ is shown to be enhanced by a cholesterol-rich environment (Raffai and Weisgraber, 2003). A report from an epidemiological study on a large cohort of women and men has demonstrated that high cholesterol levels during mid-life are associated with a 66% increase in AD risk late in life (Solomon et al., 2009). These findings suggest that the plasma cholesterol level in our 40s determines our degree of risk for AD. At later age, when AD progresses, plasma cholesterol levels do not appear to correlate with progression of dementia-with patients having either normal, low or high plasma cholesterol levels. In addition to cholesterol, altered levels of sphingolipidome, ceramides and several phospholipids levels may be involved in AD. There is also increasing evidence that saturated free fatty acids (FFA) increase the risk of AD (Bazan et al., 2011). More recently, a set of lipids from peripheral blood was discovered to predict conversion to AD with over 90% accuracy (Mapstone et al., 2014). All together, these studies suggest that lipids, including cholesterol, can influence the pathogenesis of AD. However, the question as to how cholesterol contributes to AD remains to be answered. The difficulty in understanding the role of high plasma cholesterol in AD pathogenesis emanates from the facts that (i) the brain makes its own cholesterol and (ii) little or no plasma cholesterol enters into the brain to induce AD pathology because of the impermeability of the blood brain barrier (BBB).

Several hypotheses can be advanced to explain how high levels of cholesterol in plasma can trigger neurodegeneration in the brain. *First*, the BBB integrity in AD is very likely to be compromised and we have shown that a diet rich in cholesterol makes the BBB leaky (Chen et al., 2008). *Second*, fluctuations in levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), rather than cholesterol per se, may correlate better with the progression of AD. Indeed, high LDL-C and low HDL-C levels were found to be associated with cerebral amyloidosis in humans (Reed et al., 2014), and high HDL-C levels have also been shown to correlate with a lower risk of late onset AD in elderly individuals (Reitz et al., 2010). *Third*, it may also be possible that cholesterol oxidized products (oxysterols) may represent the link between peripheral cholesterol and the neuropathology of AD in the brain. This review will provide data from our laboratory demonstrating a potential link between oxysterols and AD-like pathology in animal models.

We have been studying the potential association between cholesterol metabolism and the development of Alzheimer's disease (AD)-related pathology in cell cultures, in rabbit brains and in organotypic slices from adult rabbit brains for the last ten years. The following are results we obtained that (a) strongly suggest that cholesterol is linked to AD-like pathology, (b) shed light on oxysterols as the link between plasma cholesterol and AD-like pathology, and (c) identify cellular mechanisms involved in cholesterol and oxysterol-induced AD-like pathology.

3.1. Cholesterol-enriched diets increase plasma cholesterol, induce AD-like pathology but does not affect brain cholesterol levels

The cholesterol-fed rabbit was initially used as a model for experimental atherosclerosis by Nikolaj Anitschkow in 1913 and was later found by Sparks and coleagues to exhibit Aβ plaques (Sparks et al., 1994). We have also demonstrated that, in addition to increasing Aβ, cholesterol-enriched diets increase tau phosphorylation and oxidative stress in rabbits (Ghribi et al., 2006a,b). Additionally, the eye blink classical conditioning that is impaired in AD patients is also impaired in the rabbit model (Schreurs et al., 2012; Woodruff-Pak et al., 2007). Furthermore, rabbits have a phylogeny closer to humans than rodents (Graur et al., 1999), and their Aβ sequence, unlike that of rodents, is similar to the Aβ sequence of the human (Johnstone et al., 1999). All these findings suggest that the cholesterol-fed rabbit is a relevant model for sporadic AD studies, as it is a unique model system that exhibits the major pathological hallmarks of AD without genetic manipulations. Thus, this

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